International Journal of Drug Delivery 3 (2011) 305-314
http://www.arjournals.org/index.php/ijdd/index
Original Research Article
ISSN: 0975-0215

Design and evaluation of sustained release matrix tablets of levofloxacin for effective treatment of microbial infections

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Abstract

The objective of present work was to formulate and evaluate sustained release matrix tablets of levofloxacin for treating microbial infections effectively. Levofloxacin is the active component of the racemate ofloxacin, and used for treating a variety of clinical conditions such as lower respiratory tract infections, acute sinusitis, uncomplicated skin and soft-tissue infections and complicated urinary tract infections. Different formulations were prepared by wet granulation method using various release rate controlling hydrophilic polymers. The formulations were evaluated for hardness, weight variation, friability and drug content uniformity. The in vitro release of drug from the formulations was studied in pH 1.2 acidic buffer and pH 6.8 phosphate buffer, and it was found that the prepared tablets were able to sustain the release of the drug. The release of levofloxacin from the tablets was diffusion controlled and the release mechanism was non-Fickian. For conclusion, the developed formulations may reduce the dosing intervals, reduce the dose related side effects and increase the drug's efficacy for treating infections.

Keywords: Matrix tablets, levofloxacin, HPMC, guar gum, xantham gum, locust bean gum, Amorphophallus starch.

Introduction

Though, Dr. Paul Ehrlich's concept of 'magic bullet' realized late, helps to solve the problems of unwanted side effects of drugs and optimizing the therapy in its true sense. The sustained and controlled release drug delivery can be considered as the progenitor of magic bullet concept [1]. The main objective of developing a sustained release dosage form is to maintain drug concentration in the blood for a prolonged period of time, which results reduction in dosing interval and reduce the dose related side effects. Drugs with low therapeutic index and short half life are ideal candidates for sustained drug delivery [2]. Oral route is the most convenient route for the administration of drugs. This is because of more flexibility in dosage form design for oral route than for parenteral or any other route. Oral sustained release dosage forms such as matrix tablets have been getting much attention by the researches due to several advantages [3]. Many drugs are available in the market as sustained release tablets due to the fact that they are usually easy and economical to formulate, greater acceptance by the people and greater patient compliance.

Sustained release matrix tablets can be formulated using hydrophilic polymers such as hydroxy propyl methyl cellulose (HPMC), guar gum, xantham gum, locust bean gum, sodium carboxy methyl cellulose, sodium alginate, etc.

[4]. The release of drug from the matrix tablets formulated with hydrophilic polymers can be controlled by polymer swelling and cross-linking [5]. Many studies have been carried out to find out the effectiveness of hydrophilic polymers to fabricate sustained release matrix tablets to deliver hydrophilic and hydrophobic drugs [4,6]. Hydroxy propyl methyl cellulose, semisynthetic nonionic cellulose ether, is widely used in controlled-release dosage forms due to its versatility, nontoxic nature, and its pH independence.

Fluoroquinolones are synthetic antibacterial agents. They have received much attention recently by researches owe to their ability to treat a wide range of infections. Nalidixic acid, the first fluoroquinolone, was introduced in 1962 [7]. Subsequently, numerous nalidixic acid derivatives have been introduced to treat a wide range of bacterial infections [8]. Levofloxacin is one among them and has wider clinical usage. It is the pure (-)-(S)-enantiomer of the racemate ofloxacin [9]. Levofloxacin inhibits bacterial cell division by inhibiting DNA gyrase, bacterial type II topoisomerase, and topoisomerase IV. It is rapidly and completely absorbed after oral administration. It has a half life is 6 to 8 h. It has been used for treating various conditions such as pneumonia, chronic bronchitis and sinus, urinary tract, kidney, prostate and skin infections [10]. The development of oral sustained release matrix tablets of levofloxacin is highly useful considering the above said facts. This is expected to maintain drug concentration in the blood for a prolonged period of time which inturn reduce the dosing intervals and increase patient compliance. Hence the present work was undertaken with an objective of to formulate and evaluate sustained release matrix tablets of levofloxacin for treating microbial infections in an effective manner.

Materials and methods

Materials

Levofloxacin was a kind gift from Cadila Pharmaceuticals, Ahmadabad, India. Hydroxy propyl methyl cellulose was purchased from Otto chemicals, India. Amorphophallus starch was obtained as a gift from Central Tuber Crops Research Institute, Thiruvananthapuram, India. Microcrystalline cellulose (Avicel PH 102) was a kind gift from Strides Arco Lab., Bangalore, India. All other chemicals used for the study were analytical grade.

Methods

Preparation of levofloxacin tablets

Levofloxacin tablets were prepared by wet granulation method. Specified quantity of drug, polymer (HPMC or guar gum or xantham gum or locust bean gum or Amorphophallus starch) and Avicel PH 102 were weighed (Table 1) and mixed thoroughly. The powder mixture was converted into a sluggy mass using 5% starch paste. Granules were obtained by passing the sluggy mass through sieve no 12. The prepared granules were subjected to drying at 40^{o}C for 4 h. After drying, the granules were screened through sieve no 22 & 44 and stored for further studies. Specified quantity of magnesium stearate and talc was finally added into the granules and mixed thoroughly. The mixture was directly punched into tablets weighing about 300 mg containing 100 mg of levofloxacin, using rotary tablet compression machine (12 stations, Karnavati, India), using 9 mm diameter concave punches. The different batches of levofloxacin tablets were collected and stored in air tight containers.

Evaluation of granules

Determination of granules size by optical microscopy

Mean granules size was determined using optical microscopy. For this, the granules were evenly spread on a glass slide. Granules size was determined by measuring the individual granules along the longest axis and the shortest axis (cross shaped measurement) using an optical microscope after calibration. Average of these two readings is the mean diameter of granules. In each batch, the diameter of minimum 50 granules was determined.

Table 1. Formula for the preparation of levofloxacin sustained release matrix tablets.

Batch code	Ingredients									
	Drug (mg)	HPMC (mg)	AS (mg)	GG (mg)	XG (mg)	LBG (mg)	MCC (mg)	SP (5%)	MS (mg)	Talc (mg)
F-1	100	-	-	-	-	-	191	q.s	6	3
F-2	100	30	-	-	-	-	161	q.s	6	3
F-3	100	60	-	-	-	-	131	q.s	6	3
F-4	100	90	-	-	-	-	101	q.s	6	3
F-5	100	120	-	-	-	-	71	q.s	6	3
F-6	100	150	-	-	-	-	41	q.s	6	3
F-7	100	-	30	-	-	-	161	q.s	6	3
F-8	100	-	60	-	-	-	131	q.s	6	3
F-9	100	-	90	-	-	-	101	q.s	6	3
F-10	100	-	120	-	-	-	71	q.s	6	3
F-11	100	-	150	-	-	-	41	q.s	6	3
F-12	100	-	-	30	-	-	161	q.s	6	3
F-13	100	-	-	60	-	-	131	q.s	6	3
F-14	100	-	-	90	-	-	101	q.s	6	3
F-15	100	-	-	120	-	-	71	q.s	6	3
F-16	100	-	-	150	-	-	41	q.s	6	3
F-17	100	-	-	-	30	-	161	q.s	6	3
F-18	100	-	-	-	60	-	131	q.s	6	3
F-19	100	-	-	-	90	-	101	q.s	6	3
F-20	100	-	-	-	120	-	71	q.s	6	3
F-21	100	-	-	-	150	-	41	q.s	6	3
F-22	100	-	-	-	-	30	161	q.s	6	3
F-23	100	-	-	-	-	60	131	q.s	6	3
F-24	100	-	-	-	-	90	101	q.s	6	3
F-25	100	-	-	-	-	120	71	q.s	6	3
F-26	100	-	-	-	-	150	41	q.s	6	3

HPMC- hydroxypropyl methylcellulose; AS- Amorphophallus starch; GG- guar gum;
XG- xanthum gum; LBG- locust bean gum; MCC- microcrystalline cellulose; SP- starch paste; MS- magnesium stearate; q.s- quantity sufficient.

Determination of bulk density

Bulk density was determined by using bulk density apparatus. It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed granules into the graduated measuring cylinder of the bulk density apparatus and the volume was noted.

Determination of tapped density

Tapped density is the ratio of total mass of powder to the tapped volume of powder. This was measured by tapping the powder to constant volume.

Determination of Carr's index and Hausner's ratio

The flow properties of granules are indicated by Carr's index. It is given in percentage and determined by the formula $(D_t\text{-}D_b/D_t) \times 100$; where D_t is the tapped density and D_b is the bulk density. The Hausner's ratio is determined by the following formula (D_t/D_b).

Determination of angle of repose

Angle of repose is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. This was determined by

passing required quantities of levofloxacin granules through a funnel from a particular height (2 cm) onto a flat surface until it formed a heap, which touched the tip of the funnel. The height and radius of the heap were measured. The angle of repose was determined by using the formula; Angle of repose, $\theta = \tan^{-1}(h/r)$; where, h-height of the pile in cm and r-radius of the pile.

Evaluation of sustained release matrix tablets of levofloxacin

Hardness

The hardness of different batches of prepared tablets was tested by using Monsanto hardness tester and given in kg/cm^2.

Weight variation test

For this, 20 tablets were taken randomly from each batch and weighed separately, and the average weight was determined. The weight variation was determined by calculating the percent deviation of each tablet's weight against the average weight according to the official method [11].

Friability

Twenty tablets were taken from each batch randomly and the friability was determined using Roche Friabilator and expressed in percentage.

Drug content uniformity

The prepared levofloxacin tablets were tested for their drug content. Six tablets of each batch were finely powdered; 100 mg of powder was accurately weighed and the drug was completely extracted with pH 1.2 acidic buffer. The solution was filtered and the levofloxacin content was determined by UV spectrophotometer (Shimadzu (UV-1700), Japan) at 293 nm.

In vitro drug release studies

The release of drug from different batches of prepared tablets was studied by using USP dissolution apparatus type II [12]. The dissolution medium used was 900 ml of acidic buffer of pH 1.2 for 2 h and phosphate buffer of pH 6.8 for 10 h. The temperature was maintained at 37°C ± 0.5°C and the stirring rate was 100 rpm. Samples were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV Spectrophotometer at 293 nm against a blank.

Release kinetics

The in vitro release data of drug levofloxacin from selected formulations (F5, F16, F20 and F26) were fitted to various kinetic equations such as zero order, first order, Higuchi and Korsmeyer-Peppas release kinetics model [13]. For zero order ($Q = Q_0 - K_0 t$) the graph was plotted in cumulative percent of drug released Vs time, first order release ($\ln Q = \ln Q_0 - K_1 t$) the graph was plotted in log cumulative percent of drug remaining vs time. In the case of Higuchi ($Q = K_2 t^{1/2}$) the graph was plotted in cumulative percent of drug released vs squre root of time, and for Korsmeyer-Peppas ($Q/Q_0 = K t^n$) the graph was plotted in log cumulative percent of drug released vs log time. Where, K_0 to K_2 were release rate constants, Q/Q_0 was fraction of drug released at time t, K was a constant and n was diffusion constant that indicates general operating release mechanism.

Results & discussion

Characterization of levofloxacin sustained release matrix tablets

Pre-compression parameters

Granulation is an important step in the preparation of tablets as the physical properties of granules play a vital role in the release of drug from the sustained release tablets. The levofloxacin granules were prepared by wet granulation method. The prepared granules of different batches were evaluated for their granules size, angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio, and the results are shown in Table 2. The granules have an average size in the range of 0.448 ± 0.11 to 0.683 ± 0.15 mm, which indicates narrow size distribution. The bulk densities of the granules were found to be in the range of 0.400 to 0.48 gm/ml. The angle of

repose varied from 27.51 ± 0.18° to 31.37 ± 0.18°. The low values of angle of repose indicate the free flowing nature of the granules. The tapped densities were ranged 0.444 to 0.545 gm/ml and the Carr's indexes were in the range of 9.05 to 13.53. Hausner's ratio was found in the range of 1.02 ± 0.04 to 1.15 ± 0.09 and the values showed the low interparticle friction between the granules. The values of compressibility index further confirmed the good compressibility of the prepared granules [14,15].

Post-compression parameters

The tablets of levofloxacin were prepared by wet granulation method. The prepared tablets were evaluated for their weight variation, hardness, friability and drug content uniformity, and the results are presented in Table 3. The weight variation was within the prescribed limits and it was varied between 0.09 ± 0.024 to 1.4 ± 0.02 %. Hardness was in the range of 4.5 ± 0.14 to 7.7 ± 0.35 kg/cm^2. Friability was less than 1% in all the batches, which indicates tablet's ability to withstand shock during the time of transportation and handling. Drug content was uniform within the prepared batches and ranged between 72.87 ± 0.34 to 96.84 ± 0.16%. It is clear from the above said factors that the physical parameters evaluated for the different batches of tablets were within the prescribed limits [11].

Table 2. Physical evaluation of levofloxacin granules

Batch Code	Parameter					
	Mean size (mm)**	Bulk density (gm/ml)*	Tapped density (gm/ml)*	Carr's Index (%)	Hausner's ratio	Angle of repose (°)*
F-1	0.66 ± 0.25	0.40 ± 0.06	0.444 ± 0.05	10.01 ± 0.14	1.11 ± 0.06	29.05 ± 0.25
F-2	0.683 ± 0.15	0.480 ± 0.03	0.545 ± 0.03	11.92 ± 0.12	1.13 ± 0.02	29.74 ± 0.24
F-3	0.575 ± 0.12	0.440 ± 0.04	0.500 ± 0.02	12.00 ± 0.15	1.13 ± 0.05	27.75 ± 0.15
F-4	0.570 ± 0.16	0.432 ± 0.05	0.490 ± 0.04	11.83 ± 0.13	1.13 ± 0.03	29.74 ± 0.17
F-5	0.520 ± 0.05	0.416 ± 0.03	0.476 ± 0.05	12.60 ± 0.09	1.14 ± 0.04	29.05 ±0.26
F-6	0.530 ± 0.21	0.409 ± 0.04	0.473 ± 0.03	13.53 ± 0.24	1.15 ± 0.09	29.30 ± 0.14
F-7	0.539 ± 0.06	0.412 ± 0.04	0.460 ± 0.05	10.43 ± 0.20	1.11 ± 0.07	29.60 ± 0.34
F-8	0.612 ± 0.04	0.420 ± 0.03	0.466 ± 0.06	9.87 ± 0.14	1.10 ± 0.06	28.52 ± 0.14
F-9	0.448 ± 0.11	0.421 ± 0.05	0.476 ± 0.04	11.55 ± 0.07	1.13 ± 0.03	29.05 ± 0.26
F-10	0.536 ± 0.05	0.408 ± 0.03	0.450 ± 0.05	9.30 ± 0.17	1.10 ± 0.08	27.51 ± 0.18
F-11	0.659 ± 0.20	0.412 ± 0.05	0.454 ± 0.03	9.20 ± 0.23	1.07 ± 0.04	30.76 ± 0.21
F-12	0.538 ± 0.16	0.410 ± 0.02	0.463 ± 0.03	11.64 ± 0.18	1.12 ± 0.07	30.76 ± 0.36
F-13	0.507 ± 0.04	0.400 ± 0.02	0.444 ± 0.06	10.01 ± 0.32	1.11 ± 0.03	29.60 ± 0.12
F-14	0.488 ± 0.15	0.420 ± 0.03	0.474 ± 0.03	11.49 ± 0.12	1.12 ± 0.02	29.05 ± 0.24
F-15	0.545 ± 0.12	0.411 ± 0.05	0.456 ± 0.02	10.01 ± 0.15	1.10 ± 0.05	28.52 ± 0.15
F-16	0.537 ± 0.06	0.418 ± 0.05	0.472 ± 0.04	11.44 ± 0.13	1.12 ± 0.03	29.60 ± 0.17
F-17	0.542 ± 0.05	0.405 ± 0.03	0.450 ± 0.05	9.05 ± 0.09	1.06 ± 0.04	30.71 ± 0.26
F-18	0.535 ± 0.21	0.411 ± 0.04	0.455 ± 0.03	9.60 ± 0. 24	1.10 ± 0.09	29.05 ± 0.14
F-19	0.539 ± 0.06	0.430 ± 0.04	0.485 ± 0.05	11.34 ± 0.20	1.12 ± 0.07	29.60 ± 0.34
F-20	0.515 ± 0.04	0.415 ± 0.03	0.459 ± 0.06	9.50 ± 0.14	1.10 ± 0.06	28.52 ± 0.14
F-21	0.560 ± 0.11	0.411± 0.05	0.455 ± 0.04	9.60 ± 0.07	1.10 ± 0.03	28.00 ± 0.26
F-22	0.560 ± 0.15	0.405 ± 0.03	0.457 ± 0.05	11.47 ± 0.17	1.12 ± 0.08	31.37 ± 0.18
F-23	0.559 ± 0.12	0.400 ± 0.05	0.451 ± 0.03	11.32 ± 0.23	1.12 ± 0.04	30.17 ± 0.21
F-24	0.530 ± 0.06	0.414 ± 0.02	0.457 ± 0.03	9.40 ± 0.18	1.10 ± 0.07	29.60 ± 0.36
F-25	0.517 ± 0.04	0.418 ± 0.02	0.472 ± 0.06	11.44 ± 0.32	1.12 ± 0.03	29.60 ± 0.12
F-26	0.475 ± 0.05	0.424 ± 0.07	0.477 ± 0.04	11.42 ± 0.06	1.13 ± 0.05	29.05 ± 0.07

***** (n=3 ± S.D) ****** (n=50 ± S.D)

Table 3. Physicochemical evaluations of pantoprazole tablets

Batch Code	Parameter			
	Hardness (kg/cm^2)*	Friability (%)**	Weight variation (%)**	Drug content (%)***
F-1	5.8 ± 0.4	0.012 ± 0.03	1.1 ± 0.05	91.23 ± 0.05
F-2	7.4 ± 0.01	0.015 ± 0.02	1.4 ± 0.02	81.5 ± 0.21
F-3	5.7 ± 0.12	0.010 ± 0.02	0.96 ± 0.01	78.2 ± 0.15
F-4	7.7 ± 0.35	0.018 ± 0.03	0.859 ± 0.01	72.87 ± 0.34
F-5	6.3 ± 0.21	0.005 ±0.03	0.09 ± 0.02	96.5 ± 0.42
F-6	5.9 ± 0.15	0.020 ± 0.02	0.65 ± 0.03	96.84 ± 0.16
F-7	5.7 ± 0.42	0.10 ± 0.02	0.43 ± 0.02	94.93 ± 0.09
F-8	6.5 ± 0.17	0.12 ± 0.03	0.19 ± 0.02	92.87 ± 0.48
F-9	5.4 ± 0.16	0.6 ± 0.04	0.29 ± 0.01	83.97 ± 0.26
F-10	6.7 ± 0.24	0.40 ± 0.02	0.14 ± 0.01	91.36 ± 0.35
F-11	5.9 ± 0.25	0.16 ± 0.02	0.56 ± 0.02	86.9 ± 0.42
F-12	5.8 ± 0.34	0.27 ± 0.03	0.98 ± 0.02	94.15 ± 0.13
F-13	6.0 ± 0.18	0.33 ± 0.03	0.132 ± 0.03	92.15 ± 0.18
F-14	5.0 ± 0.09	0.33 ± 0.03	0.234 ± 0.04	86.15 ± 0.38
F-15	6.5 ± 0.24	0.16 ± 0.02	0.287 ± 0.02	90.76 ± 0.27
F-16	7.0 ± 0.08	0.16 ± 0.02	0.290 ± 0.01	86.72 ± 0.36
F-17	5.0 ± 0.13	0.1 ± 0.01	0.76 ± 0.02	94.05 ± 0.15
F-18	6.0 ± 0.05	0.4 ± 0.01	0.56 ± 0.04	92.00 ± 0.5
F-19	5.5 ± 0.24	0.33 ± 0.05	0.54 ± 0.63	86.10 ± 0.04
F-20	5.7 ± 0.13	0.27 ± 0.04	0.75 ± 0.03	89.76 ± 0.08
F-21	6.5 ± 0.12	0.33 ± 0.01	0.76 ± 0.02	85.72 ± 0.04
F-22	4.5 ± 0.14	0.33 ± 0.07	0.86 ± 0.04	94.15 ± 0.06
F-23	5.0 ± 0.05	0.27 ± 0.01	0.56 ± 0.03	90.15 ± 0.07
F-24	5.5 ± 0.12	0.33 ± 0.01	0.05 ±.0.02	86.15 ± 0.02
F-25	6.0 ± 0.04	0.15 ± 0.01	0.3 ± 0.03	91.76 ± 0.05
F-26	5.5 ± 0.05	0.16 ± 0.02	0.12 ± 0.02	86.72 ± 0.05

*(n=6 ± S.D) **(n=20 ± S.D) ***(n=3 ± S.D)

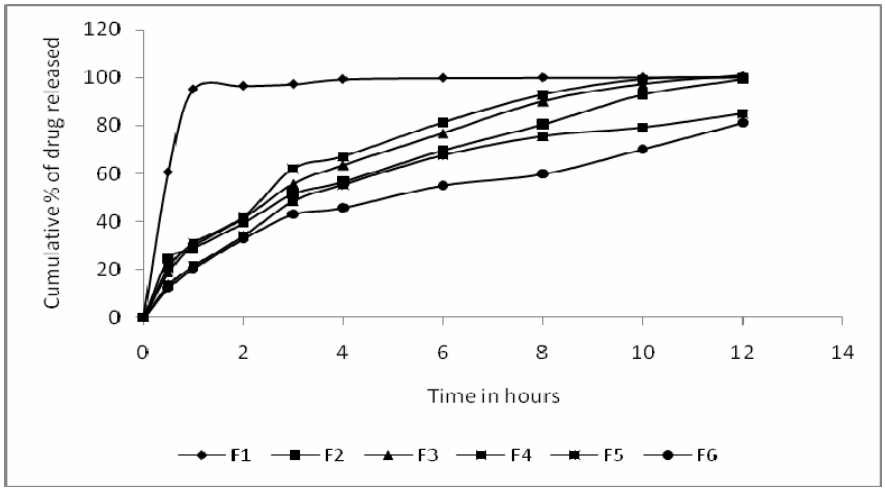

Figure 1. *In vitro* drug release profile of levofloxacin from tablet formulations F1 to F6.

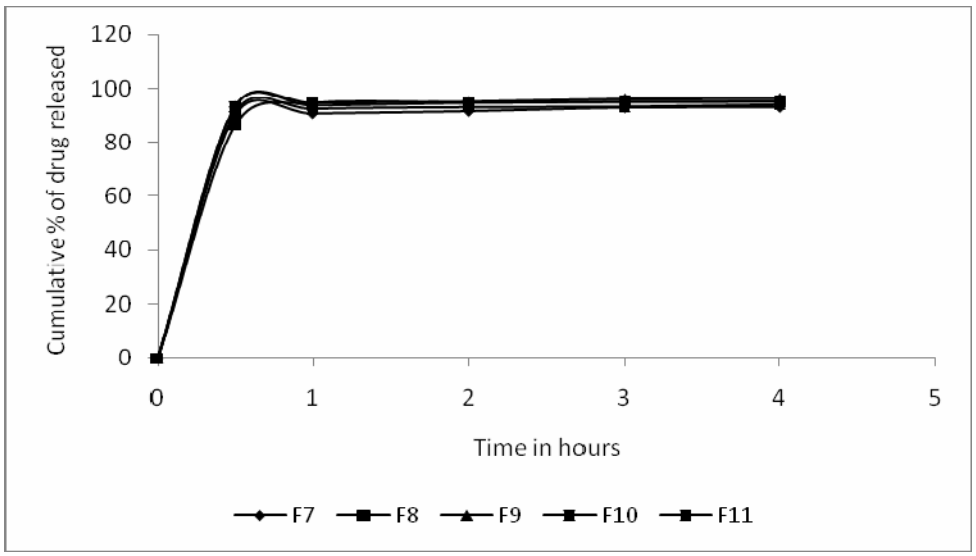

Figure 2. *In vitro* drug release profile of levofloxacin from tablet formulations F7 to F11.

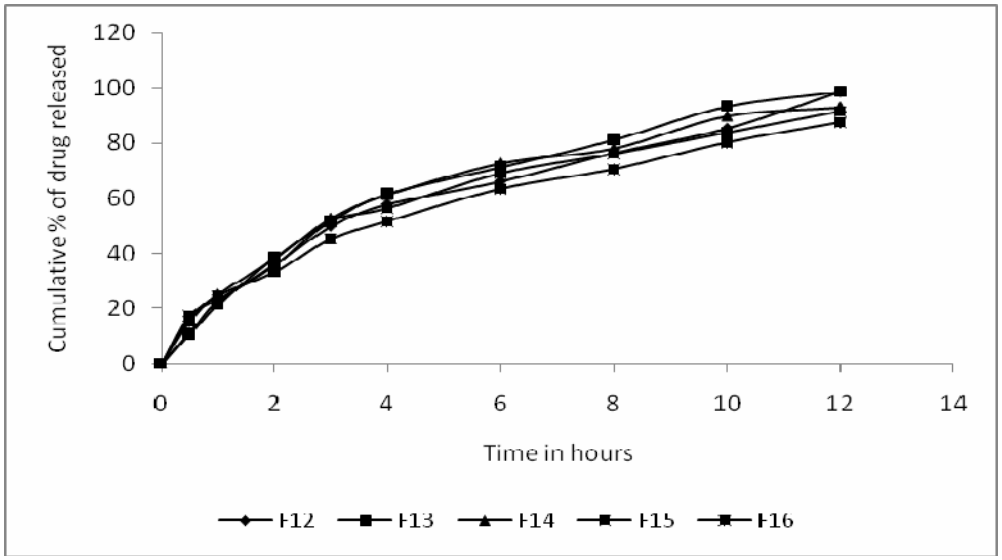

Figure 3. *In vitro* drug release profile of levofloxacin from tablet formulations F12 to F16.

In vitro drug release studies

Studying the release of drug from the tablets is important to know about the drug release pattern. Release of drug from a sustained release matrix tablets is affected by many factors which includes the granulation method, type of additives used, drug polymer ratio, pH of the dissolution medium and drug solubility in the dissolution medium [16]. The in vitro release was studied in pH 1.2 acidic buffer for 2 h and in phosphate buffer pH 6.8 for 10 h. The release was affected by the type of polymer as well as the concentration used (Figure 1 to Figure 5). As expected, Formulation-1 released about 95% of its contents within an hour due to the fact that it was prepared without release controlling polymer. All the polymers except Amorphophallus starch extended the drug release over a prolonged period of time and the drug release from the tablets also depend on the nature and concentration of the polymer used. Among the formulations, F5, F16, F20 and F26 have showed maximum sustained release.

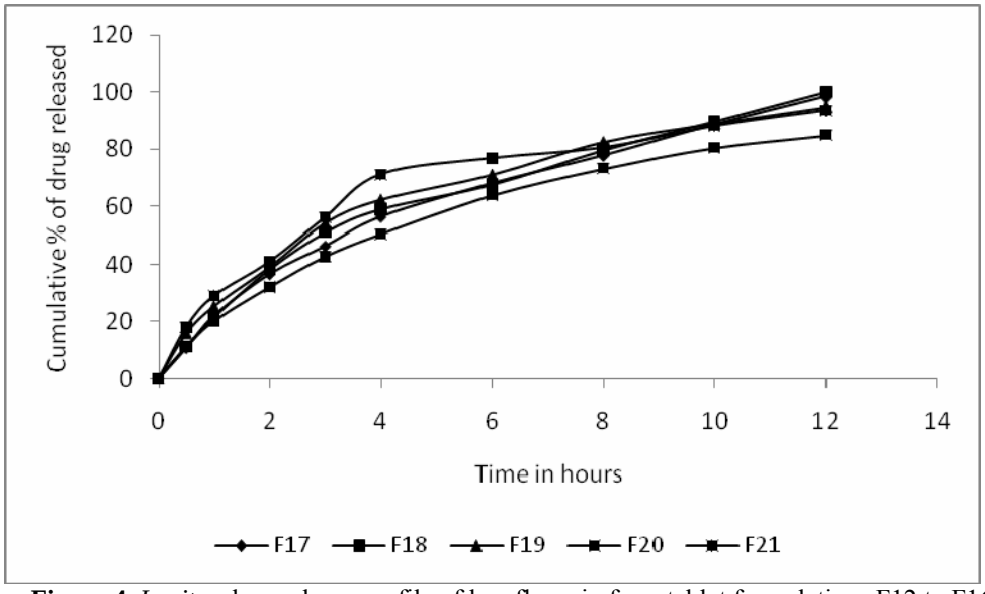

Figure 4. *In vitro* drug release profile of levofloxacin from tablet formulations F12 to F16.

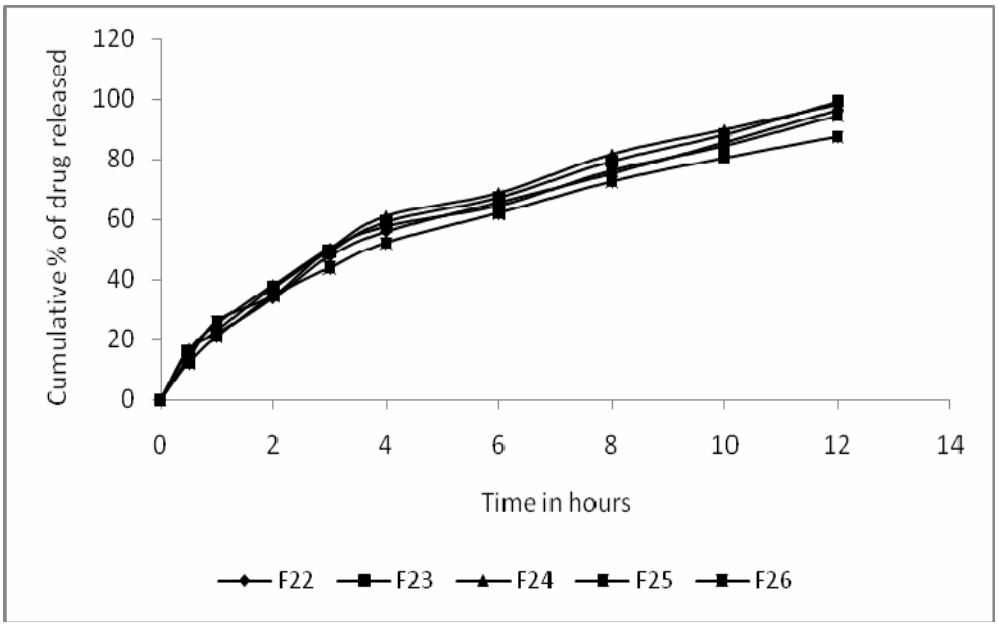

Figure 5. *In vitro* drug release profile of levofloxacin from tablet formulations F22 to F26.

Table 4. Release kinetics of levofloxacin from tablet formulations.

Formulation	Zero order r^2	First order r^2	Higuchi r^2	Korsmeyer-Peppas	
				r^2	n
F-5	0.943	0.970	0.986	0.981	0.559
F-16	0.952	0.990	0.996	0.994	0.540
F-20	0.934	0.991	0.993	0.987	0.635
F-26	0.942	0.993	0.996	0.988	0.606

Release kinetics

The in vitro release data obtained from Formulations- F5, F16, F20 and F26 was fitted to kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas models [13] to explore the release mechanism and the values are given in Table 4. The data obtained from the release kinetics fitted with Higuchi model indicated that the release of drug from the tablets was depend on the square root of time. Further, it is important to note that a linear relationship was obtained for a plot of release profile verses time, and the regression coefficient was very close to zero (r^2 = 0.986, 0.996, 0.993 and 0.996 for Formulations- F5, F16, F20 and F26 respectively) for all the four formulations. The n values obtained from the Korsmeyer-Peppas model showed that the release mechanism was non-Fickian. Generally, tablets prepared with hydrophilic polymers show a release mechanism of Fickian indicating the passage of drug through the polymer matrix by diffusion. But, sometimes other factors such as rate of polymer swelling, polymer chain relaxation also influence the drug release in addition to diffusion and lead to non-Fickian mechanism [17].

Conclusion

The sustained drug release can be obtained by hydrophilic polymers such as HPMC, guar gum, xantham gum and locust bean gum. Amorphophallus starch failed to prolong levofloxacin release from the tablets. The drug release also depends on the concentration and the nature of polymer. The drug release was diffusion controlled and the release mechanism was non-Fickian. Though further in vivo studies are required to confirm the effectiveness of the prepared formulations, it can be concluded that the prepared formulations may reduce the dosing intervals, reduce the dose related side effects and increase the drug's efficacy for treating various bacterial infections.

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